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Review Article (Pages: 11197-11217)

Quality of Life in Patients with Thalassemia Major: A Concept Analysis Using Rodgers' Evolutionary Method

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Abstract

Background: Quality of life (QoL) is a complicated phenomenon in patients with thalassemia major. This study was conducted to clarify the concept of QoL in patients with thalassemia major.

Materials and Methods: This study was performed using Roger's evolutionary method. Electronic databases: Cochrane Library, Web of Science, Scopus, Science Direct, ProQuest, and Medline. The inclusion criteria were papers published in English up to March 2017 with no time limit for publication. The keywords searched in titles, abstracts, and keywords of the studies included quality of life, health-related quality of life, thalassemia, thalassemia major, beta thalassemia, and beta thalassemia major.

Results: 67 studies were included. QoL in most studies had been evaluated using the SF-36 and PedsQL. The terms QoL, HRQoL, and QL were used interchangeably in most of the studies. In this concept analysis, HRQoL and well-being were recognized as surrogate terms for the QoL in patients with thalassemia major. The concepts related to the QoL in patients with thalassemia major included satisfaction, indicator of health care, individual's own view of health, and health status assessment. Five antecedents identified in this concept analysis were: professional figure mainly involved, clinical-care interventions, medicinal and therapeutic approaches and response to them, disease characteristics and presence of comorbidities, ability and characteristics of patient. Seven attributes of the QoL in patients with thalassemia major were objective, subjective, multidimensional, measurable, dynamic, predictable, and processable.

Conclusion: Consequences of the concept were effects on physical functioning and improvement of psychological conditions, compliance with regular chelation therapy, iron overload, continuing education, having an appropriate job and marriage, patients' economic and social status, and finally, motivation and life expectancy.

Key Words: Beta-thalassemia, Concept analysis, Rodgers evolutionary method, Quality of life.

*Please cite this article as: Arian M, Soleimani M, Fakhr-Movahedi A, Oghazian MB, Badiee Z. Quality of Life in Patients with Thalassemia Major: A Concept Analysis Using Rodgers' Evolutionary Method. Int J Pediatr 2020; 8(5): 11197-217. DOI: **10.22038/ijp.2019.42126.3547**

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Received date: Aug.23, 2019; Accepted date: Feb.12, 2020

1- INTRODUCTION

Thalassemias are autosomal recessive hereditary disorders. The synthesis of beta chain of hemoglobin is not enough in beta-thalassemia. Beta-thalassemia major (BTM) is the severest type of thalassemia. BTM is more prevalent in Mediterranean regions, parts of North and West Africa, Middle East, Indian Peninsula, and Southeast Asia, which are collectively known as the thalassemia belt. Almost 3% of people in the world are carriers of b-thalassemia gene (1). BTM is dispersed in almost all Arabian countries at different rates with the carrier rate 1 to 11%. It is more frequent in Lebanon, Jordan, Iraq, Palestine, and Egypt. There are 20,000 patients or pediatrics with thalassemia only in Iran (2). The nature of thalassemia is such that it greatly affects the quality of life (QoL) of pediatrics with thalassemia (3). The need for regular visits for blood transfusion and the difficult regimen of subcutaneous injection of chelators are frightful and worrisome for children with thalassemia major and their family.

QoL in these patients is lower than that of their normal peers. The duration of the disease and long course of treatment, frequent hospitalizations, high costs of treatment, mental status, and social harms cause stress in these pediatric patients and their families. The introduction of methods, such as the regular blood transfusion and intake of effective chelators with deferoxamine over the last 30 years has considerably improved their QoL (4). Although the mortality rate of pediatrics with thalassemia major has diminished in light of modern medical treatments, new treatment approaches in these patients may affect different aspects of their life. The reduced mortality and increased life expectancy have left these patients with newer challenges, such as the acquisition of higher education and job security. Infertility, difficulty in finding more effective chelators, and emergence of psychological distress have become their main concerns (5, 6). Major thalassemia and its complications have an extensive impact on QoL, which has led many researchers to assess only the general dimensions of QoL and not pay much attention to its specific dimensions. Given that the survival rate in children with thalassemia major has improved due to the development of new treatments and better clinical management (7, 8), it is important to clarify the concept of QoL and all its dimensions in these patients. Clear definitions of concepts allow researchers to identify and describe phenomena accurately. Concept analysis leads to a deep understanding and recognition of effects of a concept in clinical works and can be effective in improving the evaluation of therapies and interventions (9). Understanding the concept of QoL leads the healthcare professionals to help pediatric patients choose appropriate treatments and is likely to increase their QoL. To maintain a patient-oriented healthcare approach, the definition of healthcare-related concepts should be continuously revised regarding the pediatric patients' needs in order to discover unknown dimensions of concepts (10). To date, concept analysis has been used for the chronic obstructive pulmonary disease, lung cancer, end-stage kidney disease, critical care patients, young people with chronic diseases, and multiple sclerosis (9-16). However, concept analysis has not been performed on QoL in patients with thalassemia yet. The lack of a clear definition of QoL in these patients has led to the neglect of the problems and dimensions specific to their QoL and neglect the effects of changes in care and treatment on QoL. In a systematic review, Fulton et al. (2012) mentioned the need for stronger and more detailed studies on the concept of QoL and recognition and introduction of its determinants in special diseases (15). Without access to an appropriate definition of QoL in a

particular population, there is little hope for a better development of treatment and management methods for improving QoL. Different dimensions and interpretations have been introduced for QoL in pediatric patients with thalassemia major in the literature, and even, the terms QoL and HRQoL have been improperly used interchangeably in most cases. Chelation, transfusion, and other treatments have many psychological benefits, side effects, and consequences directly affecting patients' QoL and this is another neglected part of QoL in these patients. Regarding the high prevalence of thalassemia in Iran, this study was conducted to analyze the concept of QoL in patients with thalassemia major.

2- MATERIALS AND METHODS

2-1. Method

This article does not contain any studies with human participants performed by any of the authors. Concept or label is a brief statement that expresses the essence of a phenomenon (17). Concept development is a prerequisite for significant basic research in nursing. Concept analysis is used to develop degrees of clarification about desired concepts. A variety of concept analysis methods have been used in nursing. Roger's evolutionary method was used in this study to clarify the concept of QoL in patients with thalassemia major. The philosophical perspective of Roger's evolutionary method is used inductively to express a consensus on a concept and develop a basis for further studies (**Figure.1**). This evolutionary analysis can be used for subjects that change over time and thus is an ideal method for analysis of QoL in patients with chronic diseases (18). Based on the inductive approach of this method, raw data are collected and analyzed. Another reason for choosing this method is the evolving nature of QoL in patients with thalassemia major. Changes in QoL and its dimensions are inevitable in these patients due to the therapeutic advances. Moreover, QoL is a dynamic, developmental, and flexible process (6). Roger's evolutionary method involves 6 recurrent steps: 1) determining the desired concept, related expressions, and surrogate terms, 2) identifying and selecting the appropriate scope (samples and sets) for data collection, 3) collecting the data, related to attributes of the concept and appropriate to contextual changes, including social, cultural, interdisciplinary, and temporal changes (emergence of antecedents and consequences of the concept), 4) analyzing the data based on the concept's attributes, 5) defining an exemplar of the concept if necessary, and 6) determining hypotheses and implications for further development of the concept. Determining the desired concept is the first step researchers should take (19). Due to the changes made in QoL in pediatric patients with thalassemia following changes in the type of treatment and care as mentioned in the introduction section, researchers became interested in analysis of the concept of QoL for clarifying and identifying QoL and its dimensions in pediatric patients with thalassemia. The most important step after determining the desired concept is to determine the scope of concept in the relevant literature (19). In this study, the literature published in English (up to March 17, 2017 with no time limit for publication) about the QoL in patients with thalassemia major were analyzed. Analysis resources included Cochrane Library, Web of Science, Scopus, Science Direct, ProQuest, Medline (via PubMed) databases and Google Scholar engine (**Table.1)**. The key words searched included quality of life, health related quality of life, thalassemia, thalassemia major, beta thalassemia, and beta thalassemia major. **Table.2** shows the strategies used to search in Medline (via PubMed).

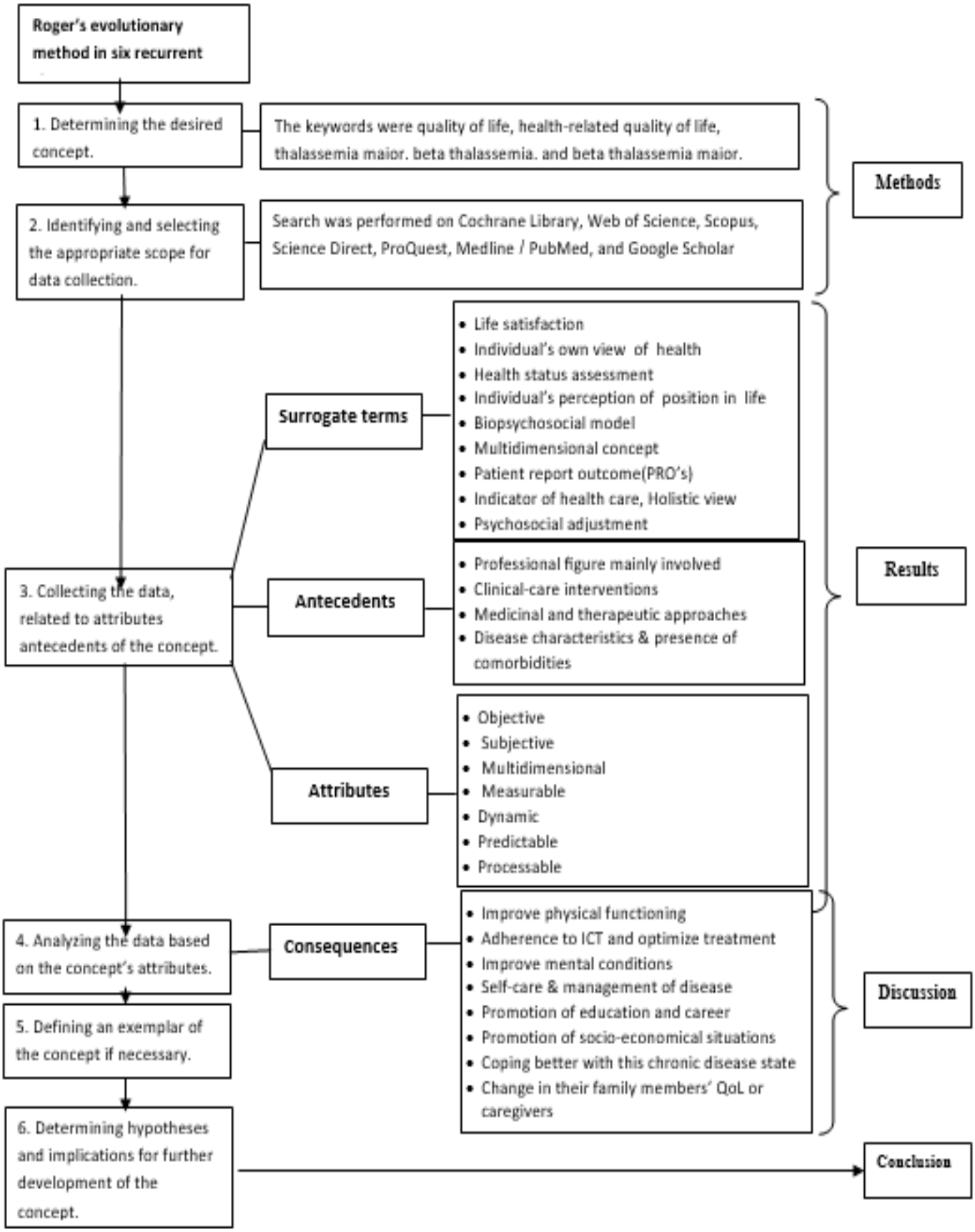

Fig.2: Concept of QoL in pediatric patients with thalassemia major by Roger's evolutionary method.

Table-1: Comprehensive review of the literature.

Cochrane Library	PubMed & Medline	Science Direct	Web of Science	Scopus	ProQuest	Ovid	Google	Total
20	356	54	103	429	117	144	16	1,239

Table-2: PubMed search strategy.

("beta-Thalassemia"[Mesh]) AND "Quality of Life"[Mesh] =50
("Thalassemia"[Mesh]) AND "Quality of Life"[Mesh]=99
(((((("thalassemia "[Title/Abstract]) OR "thalassemia major"[Title/Abstract]) OR "beta thalassemia"[Title/Abstract]) OR "beta thalassemia major"[Title/Abstract])) AND (("quality of life"[Title/Abstract]) OR "health related quality of life"[Title/Abstract])=207

Of the 1,239 studies found in searches, 710 studies were duplicates and thus were excluded from the study. The title and abstract of the remaining 529 studies were examined, and those without the terms HRQoL or QoL (360 studies) were excluded from the study. Two researchers reviewed the remaining 198 studies completely in terms of the inclusion and exclusion criteria of the study (**Table.3)**, and excluded 72 studies due to the irrelevance of their results to thalassemia major, 55 studies that had been performed on thalassemia major concurrent with sickle cell anemia, and 4 studies that overlapped with other studies. Eventually, 67 studies that were more relevant to the topic of this study were selected **Figure.2**. This process was done independently and in duplication by two reviewers and any disagreement was resolved by the third reviewer.

Table-3: Inclusion/Exclusion Criteria.

	Included	Excluded
Participants	Beta Thalassemia Major	Non- beta Thalassemia Major
Design	• Randomized controlled trials • Non-randomized controlled trials • Quasi-experimental designs (cross-sectional, cohort, longitudinal, pre-post-test) • Qualitative studies • Systematic, narrative reviews • Theses • Editorials • Opinion articles	
Objectives and Outcome	• Objectives and outcomes related to quality of life or health related quality of life in thalassemia major • Studies with a mixed patient population were included if data on beta thalassemia major patients were available, separately.	• Main theme, objective and outcomes not related to quality of life or health related quality of life in thalassemia major. • Excluded articles on quality of life of combined patients with sickle cell anemia
Language	English	Other languages
Publication	• Published • Peer-reviewed • All available (no limitation on discipline or year)	• Non-Published • Not peer-reviewed
overlapping	• Of articles with similar or overlapping researchers or articles from the same centre, we evaluated their independence by determining when, where and how many subjects were included. If more than one	• Articles were excluded if the data were provided by proxies

	published article reported data from the same subjects, the most recent article was selected, unless its sample was smaller or less information on covariates was reported. • In the case of duplication with multiple articles publishing data on the same cohort, the most complete data set or the article whose focus was more specifically on HRQOL in beta thalassemia major patients was included.	

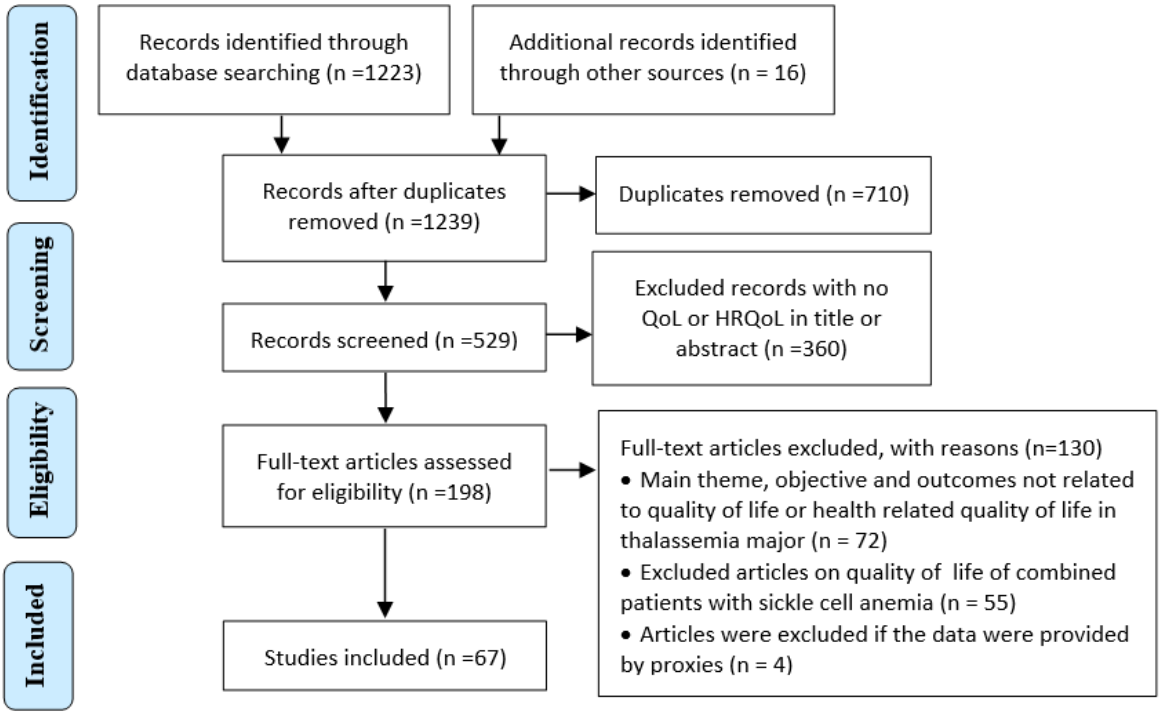

Fig.2: PRISMA flowchart.

3-RESULTS

The analysis strategy generally used in Roger's evolutionary method is the thematic analysis (19). In this study, the analysis was performed thematically similar to the content analysis. All the selected 67 studies were carefully read, and all points and items used by other researchers along with the QoL measurement instruments, areas emphasized in those studies, and the authors' recommendations for identification of dimensions of the QoL in nursing, education, and research were examined. The definitions of the concept of QoL in pediatrics with thalassemia major, attributes, antecedents, and consequences were placed under the relevant concepts and surrogate terms. The inductive approach was then used to find the main subject in each part. The researcher read the terms several times in order to immerse in them and extract the key points and labels for describing each dimension of the concept clearly. The analyzed studies had been published in 2000-2017. The 67 studies had been performed in the following countries: 15 studies (22.38%) in Iran, 12 studies (17.90%) in the USA, 7 studies (10.44%) in Italy, 4 studies (5.95%) in India, 3 studies (4.47%) in the UK, 3 studies (4.47%) in Thailand, 3 studies (4.47%) in

Greece, 3 studies (4.47%) in Malaysia, 2 studies (3%) in Saudi Arabia, 2 studies (3%) in the UAE, 2 studies (3%) in Taiwan, 2 studies (3%) in Pakistan, 2 studies (3%) in Oman, 2 studies (3%) in Maldives, 1 study (1.49%) in Jordan, 1 study (1.49%) in Lebanon, 1 study (1.49%) in Turkey, 1 study (1.49%) in Iraq, and 1 study (1.49%) in Egypt. Of the 67 studies, 26 studies (38.8%) were interdisciplinary and combined of the following teams: physicians from different specialties and/or nurses, social workers, pharmacologists, psychologists, physiotherapists, occupational therapists, behavioral scientists, epidemiologists and health policy specialists. The studies related to the area of medicine, health promotion, nursing, pharmacy, community medicine, and psychology respectively comprised 27 (40.29%), 4 (5.97%), 3 (4.47%), 3 (4.47%), 2 (3%), and 2 (3%).

3-1. Surrogate terms and related concepts

According to Roger's evolutionary method, surrogate terms are solutions for defining a concept in other words previously used in other studies (19). According to Roger, surrogate terms are in many ways similar to the desired concepts, but cover only a part of the associations and relations with that concept and do not have all its attributes (18). The terms QoL, HRQoL, and QL had been used interchangeably in the 67 studies. The frequency of using these terms is as follows: QoL in 16 studies (23.9%), HRQoL in 7 studies (10.44%), QoL and HRQoL together in 24 studies (35.82%), QL in one study (1.49%), and quality of life in 19 studies (28.35%). Generally, QoL and HRQoL had been used interchangeably in most of the reviewed studies. The World Health Organization (WHO) defines QoL as "the individuals' perceived status regarding the culture and value system where they live and is closely related to the desired goals, expectations, standards, and priorities". This definition involves the individuals' physical and mental status, degree of independence, social relations, personal beliefs, environment, and culture and is a multidimensional concept based on the individuals' culture, society, and environment; it reflects the humans' worldwide conditions, personal interests, and promotion of aspects of life, including physical, mental, political, moral, social, and spiritual aspects (20). Only Klaassen et al.'s study (2013) discussed the difference between HRQoL and QoL in patients with thalassemia major (6). According to Klaassen et al.'s study, QoL reflects the lifestyle, previous experiences, and hope for future, ambitions, and dreams, and HRQoL is the gap between individuals' expectations of health and their experiences. Klaassen et al. believe that HRQoL is related to the specific effect of a disease or illness on QoL (6).

Furthermore, HRQoL is a method in which the experimental effect of health is used to estimate QoL. HRQoL reduces the scope of QoL and focuses specifically on the effect of diseases and treatments in people's life. HRQoL does not include all aspects of QoL, such as the living environment or political stability (6). HRQoL was therefore considered a surrogate term for the concept of QoL in patients with thalassemia major in this study. In Ferrans et al.'s study, HRQoL was introduced based on a conceptual model and then as a surrogate term for the concept of QoL (21). The term "well-being" is composed of the Latin word "bene" and "stare", which mean "being well". It has been defined in the Oxford dictionary as "the state of being comfortable, healthy, or happy" (22). In the reviewed studies, well-being was mentioned as a related concept for the concepts of happiness, positive experiences or ideas, satisfaction with life, pleasure, and joy. Well-being has been

introduced as a multidimensional concept denoting the physical, mental, social, and environmental aspects of individuals. It is focused on self-care in a healthy manner and involves aspects of the awareness of physical and physiological conditions, reduction of stress, and acceptance of self-care. Well-being strategies can help individuals acquire new ways of understanding and controlling life in individual and social dimensions (1, 4, 23-35). Based on Pinto et al.'s study, several nursing theories, such as Peplau, Rogers, King, Leininger, and Parse, include the concept of QoL. Pinto et al.'s study explained the concept of QoL in Peplau's theory is a synonym of well-being or psychological health. Rogers and King introduced the concept of QoL as a synonym for life satisfaction. Leininger believes that QoL is defined based on the cultural structure, depends on cultural values, beliefs, and symbols, and indicates the strength of well-being and health promotion. Parse believes that the concept of QoL shows the meaning individuals give to their own lived experiences (36). Given that the term well-being had been defined as a synonym for QoL in 15 studies related to the QoL in pediatrics with thalassemia major (1, 4, 23-35), and regarding the perspective of nursing theories about QoL, well-being was recognized as a surrogate term for the concept of QoL in patients with thalassemia major in this study. Related concepts are terms having something in common with the desired concept without similar attributes. However, the related concept and the desired concept affect each other. The use of related concepts in the concept analysis is based on the fact that every related concept constitutes a part of a network of concepts and provides the necessary ground for expressing the importance of the desired concept. Once the related concepts are identified, the desired concept can be added to the knowledge base and clarified further (18). The related concepts identified in the analysis of the studies that were closely related to QoL with thalassemia are show in **Table.4.**

Table-4: The related concepts most commonly found in this analysis.

Related concepts	References
Life satisfaction	[30]
Individual's own view of health	[1, 4, 29, 34, 35]
Health status assessment	[1, 24, 25, 33, 37-40]
Individual's perception of position in life	[4, 6, 20, 23, 25, 26]
Biopsychosocial model	[4, 24, 26, 27, 34, 41]
Multidimensional concept	[25, 26, 35, 42, 43]
Patient report outcome (PRO's)	[6, 23, 25, 27, 38, 43, 44]
Indicator of health care	[23, 29, 30, 33, 34, 39, 45, 46]
Holistic view	[4, 30, 34]
Psychosocial adjustment	[31]

3-2. Antecedents

Antecedents are events, situations, or phenomena occurring before the desired concept occurs or are already related to the concept. Antecedents are prerequisites for the concept analyzed and affect the occurrence of concept. Roger suggests that the literature review should result in the identification of antecedents and consequences of a concept because both of them contribute to clarification of the concept (19). **Table.5** shows the antecedents in this study.

Table-5: Antecedents of QoL in Thalassemia.

Antecedents	Themes	References
Professional figure mainly involved	Health team members	[27, 30, 44, 45, 47-49]
	Nurses	[5, 23, 50]
Clinical-care interventions	Counselling programs and appointment to the psychiatric and services of social workers	[5, 20, 23, 24, 27, 30, 38, 42-44, 46, 47, 50-56]
	Health promoting behaviours	[27, 30]
	Provide health education to parents	[27, 45, 46, 51, 57]
	Maintaining functional status	[5, 25, 58]
	Holistic approach and integrated approach	[24, 50]
	Health promoting life style (HPL)	[47]
	Educational interventions about thalassemia	[23, 25, 27, 29, 43, 45, 46, 52, 54, 59]
	Cognitive behaviour family therapy (CBFT)	[27]
	Multidisciplinary approach	[33, 40, 42, 45, 46, 57, 60]
	Alternative complementary medicine	[42]
Medicinal and therapeutic approaches and response to them	Blood transfusion	[3, 4, 38, 42, 43, 47, 61-66]
	Treatment side effects	[1-3, 27, 28, 30, 35, 37, 38, 42, 43, 47, 49, 50, 53, 54, 57, 58, 62, 64, 65, 67-70]
	Subcutaneously administered Deferoxamine (DFO)	[3, 38, 44, 58, 61, 62, 65, 66, 71, 72]
	Potentially toxic oral agents	[61]
	Daily chelation therapies	[38, 43, 47, 61, 65, 66]
	Delay initiation of transfusion due to delay diagnosis	[2, 44, 67]
	Early diagnosis and start therapy at a younger age	[1, 2, 44, 67]
	DFP/DFX combination	[28]
	Increased number of days per week DFO prescribed	[39]
	Oral iron chelator, deferiprone (DFP)	[20, 29, 31, 34, 59, 69, 71]
	Adherence to ICT	[1, 2, 28, 39, 44, 56, 73]
	Non adherence to ICT	[1, 3, 23, 39, 44, 48, 72]
	Fewer hospital visits	[3, 57, 62, 67]
	Regular follow up	[23, 44, 46, 52, 62, 67]
	Timely splenectomy, up to 5 years only	[46]
	Fewer blood transfusions (<12 per year)	[69]
	Maintaining a pretransfusion Hb level, at least 9-10.5 g/dl or above 7 g/dl	[46, 60]
	Hematopoietic stem cell transplantation (HSCT)	[26, 74]
	Graft versus host disease (GvHD)	[26]
	Early detection complication	[70, 75]
	Novel therapeutic strategies	[37, 43, 49, 76]
	Lower ferritin level	[20, 44, 67]
	Iron over load(IOL)	[1, 2, 28, 38, 42, 44, 49, 60, 64, 68]
	Infection	[4]
	Infertility	[3, 48, 62]
Disease characteristics and Presence of comorbidities	Loss of physical function	[1, 33, 38, 42, 47, 49, 65, 67, 69]
	Cardiac disease(heart failure & arrhythmia)	[1, 4, 20, 28, 47, 68]
	Delay puberty	[1, 3, 4, 47, 48, 62]
	Change appearance	[3, 4, 62, 65]
	Endocrine compliance	[1, 48]
	Hepatic C	[20]
	Fatigue and weakness	[3, 30]
	Chronic pain	[33, 38, 40, 77]
	Presence of comorbidities	[2, 23, 49, 54, 67, 72]
	Cost of treatment	[61, 74]

Ability and Characteristics of patient	Un/employment	[27, 33, 42]
	Level of education	[3, 5, 42, 45, 67]
	Family history of thalassemia	[30, 52]
	Family income	[20, 34, 35, 52, 56, 65, 67]
	Higher age and reaching adulthood/lower age	[20, 23-25, 33, 38, 39, 44, 49, 69, 70, 78]
	Depression and Anxiety	[5, 23, 33, 40, 49, 51, 55, 75]
	Marriage/ Being single	[23, 33, 42]
	Gender (females)	[20, 25, 34, 73]
	Loss of physical function	[1, 33, 38, 42, 47, 49, 65, 67, 69]
	Self –management	[25]
	Poor self-image and self esteem	[3-5, 42, 62]
	Religious &spiritual growth	[2, 42, 47, 79]
	Inter-personal relations	[47]

3-2-1. Professional figures mainly involved

Nurses are pioneers in this regard. They establish appropriate care relations with children based on the patient needs and conditions, and thus affect their health status. Nurses play an important role in consultation programs and management of stress and anxiety to help pediatric patients cope with the disease and daily stressors. Nurses in some supportive, social, and advisory organizations help patients find suitable jobs and decrease therapeutic costs. They also largely contribute to following up the patients' screening through evaluating their health status constantly (5). Moreover, nurses play an important role in improvement of caring and therapeutic condition of pediatrics with thalassemia through attending the care management programs (23).

3-2-2. Clinical-care intervention

Interventions, care-education programs, and pharmaceutical program management are involved in delaying the incidence of complications, controlling symptoms, and preventing exacerbation of the disease. Reducing the symptoms and complications of the disease is directly related to physical and psychological conditions (23). Considering the effects of thalassemia on family members of these children, implementation of the family-centered empowerment model and the participation of families are very important in promoting these patients' health (45).

3-2-3. Medicinal and therapeutic approaches and response to them

Recent studies show that the new chelation therapies, especially with oral iron chelators used non-invasively, are effective in reducing the cardiac iron overload and have developed a clear perspective for the longevity of patients with thalassemia. These therapies not only improve the patients' physical condition but also affect their psychological status (37). The combination of DFP/DFX and DFP/DFO regimens reduces the iron overload, cardiac complications, and LIC and SF without causing drug toxicity (28).

A successful bone marrow transplant is the cure for these patients. Based on Caocci et al.'s study, stressors such as medications, long hospitalization for 1-2 months, isolation, continuous therapeutic preventions, and reduced age-appropriate activities demoralized, sensitized, and depressed pediatric patients at early stages of post-hematopoietic stem cell transplantation (HSCT) (26). Three months after HSCT, patients' physical and psychological condition was the same as before due to constant screening. Six months later, however, patients' health condition began to progress to the extent that their physical, psychological, social, and emotional conditions considerably improved 18 months later (26). Baraz et al.

believe that the duration of hospitalization, high costs of treatment, psychological harms after hospitalization, and screening adversely affect the physical, psychological, social, and emotional aspects of life in pediatrics and even their family (5). Hachim et al., mention that the patients whose therapeutic schedule was based on the number of transfusions (< 12 per year) were physically and mentally healthier than the group with more than 12 transfusions, and the patients receiving regular chelation therapy (≥ 30 per month), also were physically and mentally healthier than the group with fewer chelation therapies or irregular chelation therapy (73).

3-2-4. Disease characteristics and presence of comorbidities

Symptoms and characteristics of thalassemia, such as bone changes, short stature, weak body image, growth retardation, delayed puberty, severe complications and cardiac arrhythmias, liver diseases, endocrine disorders, and infections have negative effects on physical and emotional aspects and educational performance (2).

3-2-5. Ability and characteristics of patients

Coping strategies, self-management, and emotional management influence the status of pediatrics with thalassemia major (52). Clarke et al. believe that the life of pediatric patients with thalassemia will be influenced by factors, including family's economic condition and presence of another person with thalassemia in the family (a family history of thalassemia). In Clarke et al.'s study, the patients with lower economic conditions were more concerned about costs of treatment (61). Waheed et al. believe that if a child with thalassemia undergoes BTM, thalassemia management costs will decrease by 37%, and the patient's living conditions will improve (79). The presence of more than one child with thalassemia in the family negatively affects the type of treatment and the care provided by the family, and generally, a child with thalassemia of parents with only one child with thalassemia will be healthier physically and mentally (52). According to Hachim et al.'s study, getting older affects the mental, psychological, and physiological conditions of children with thalassemia. As patients grow older, they deeply perceive health and the constraints that the disease imposes on them, and compare their conditions with those of healthy children; such a comparison may cause adverse effects on the patients' mental status. Moreover, the rate of iron deposition increases as pediatric patients get older, and the complications of iron overload and repeated transfusions increase in children with thalassemia (73). In Waheed et al.'s study, faith was one of the important factors influencing the course of treatment and improvement of physical and mental conditions of children with thalassemia and their parents. The course of treatment and care of these patients is very stressful for their parents. Despite the therapeutic problems and costs in these patients, their parents (who were mostly Muslims) believed that their child's disease was God's will and a divine experiment, and God will award them for caring for their ill child. They found a child with thalassemia a "Bamaanai" (trust for safekeeping) from God (79). The parents of children with thalassemia in Abdul Wahab et al.'s study strongly believed in fate (Qada' and Qadar). However, there were some other suppositions among their beliefs. They believed that the transfer of blood donors' characteristics caused the behavioral changes of their child with thalassemia to their child through transfusion (42).

3-3. Attributes

Attributes are key repetitive features of concepts found in the relevant literature, and identification of attributes may lead to

more precise definitions of concepts (19). **Table.5** shows the seven attributes identified in this analysis: objective, subjective, multidimensional, measurable, dynamic, predictable, and processable.

3-3-1. Objective and subjective

HRQoL is the main indicator for analysis of results and consequences of treatments in patients with thalassemia (24, 34, 45). This indicator is considered a combination of subjective and objective elements (31). The World Health Organization introduces QoL as a subjective aspect presenting an individual concept in that individual himself/ herself should determine it, based on his/ her own idea, not an alternative person. In the subjective approach, QoL is influenced by individuals' experiences, beliefs, and perceptions, and individuals perceive their own situation in life in the context of cultures and values related to their goals, expectations, standards, and concerns (23). In the subjective approach, QoL evaluation is different from medical evaluation, and is focused on the individuals' perception of well-being and analysis of all aspects of life based on a holistic perspective (29). However, the concept of QoL in patients with thalassemia major is the interaction between subjective and objective approaches considering effects of the disease and treatment. The objectivity of QoL is of special importance and should not be ignored when analyzing HRQoL in patients with special diseases considering that the health status and how the disease is followed up and treated correlate with QoL (80). In children with thalassemia major, indicators of iron measurement, hemoglobin level, heart failure, liver cirrhosis, and diabetes introduce HRQoL objectively (81).

3-3-2. Multidimensional

QoL is multidimensional and is evaluated in terms of physical and social aspects, roles, pains, and mental health (25). In this study, the patients' perception of the effect of the disease was evaluated in terms of different dimensions (26, 43). The individuals' physical status, personal beliefs, social relations, psychological status, and environmental characteristics (4), affect this complicated concept.

3-3-3. Measurable

QoL is a measurable concept in the studied literature. The measurement is a way of evaluating the patients' idea about the disease and relevant treatments, health requirements, results of treatment, and consequences of the disease (25). Regarding the increased survival rate in children with thalassemia following the improvement of treatments and care practices over recent years, adherence to treatments, and use of chelation therapy at lower ages, it is of special importance to pay attention to changes in the QoL based on the above progresses, and this is possible only through measurement and appropriate instruments (1). All the available instruments evaluate QoL in terms of multiple dimensions, and some of them have been designed for general or specific purposes. TranQoL is a specific instrument for evaluating QoL in children and adult patients with thalassemia (6, 38).

STQoLI also has been developed specifically for evaluating QoL in adult patients with thalassemia (43). The instruments had been used in 52 cases of the reviewed studies as follows: SF-36 in 24 studies (46.15%) (1-3, 5, 23-25, 28, 29, 32, 37, 40, 49, 50, 54, 59, 62, 64, 65, 69, 72, 73, 75, 78); PedsQ in 15 studies (28.84%) (1, 26, 27, 30, 35, 44, 46, 52, 57, 60, 61, 67, 81-83); WHOQoL-BREF in 2 studies (3.84%) (1, 58); TranQoL in 2 studies (3.84%) (6, 38); FP-28 CHQ in 2 studies (3.84%) (39, 40); EQ-5D-3L in 2 studies (3.84%) (34, 41); SF-20 in 1 study (1.93%) (25); WHOQoL-100 in 1 study (1.93%) (4); COOP in 1 study (1.93%) (55); TQoLQ in 1 study (1.93%) (78); and STQoLI in 1 study (1.93%) (43)]. SF-36

and PedsQ had been used in most of the studies.

3-3-4. Dynamic

Although the patients' age and sex do not change, their educational level and marital status may change through multi-faceted approaches. It is necessary to know the factors influencing QoL in order to develop clinical therapeutic programs and social supports for patients with thalassemia major (23). Once the variables related to QoL are identified, the health system policymakers can develop plans for making fundamental changes in its dimensions and promoting these dimensions in children with thalassemia (25). The policymakers' supportive measures contribute to the improvement of QoL (52). Better planning based on clinical evidence helps with improvement of QoL dimensions (5). Oral chelators have highly contributed to improvement of QoL in these patients (68). Deferiprone (DFP) has been one of the dominant strategies and important achievements in changing QoL and reducing costs of treatment (71). The implementation of the family-centered empowerment model improves QoL (45). Cognitive-Behavioral Family Therapy (CBFT) also improves QoL in children with thalassemia (27). Modern therapy strategies have improved QoL through developing more comfort and bringing life closer to the normal and sensible life (31, 37). The supply of adequate healthy blood has helped with improvement of QoL (63). The formation of interdisciplinary teams consisting of hematologists, internists, endocrinologists, nurses, social workers, and psychologists have also improved QoL in patients with thalassemia (50).

3-3-5. Predictable

One of the attributes of QoL in patients with thalassemia major is its predictability. The status of HRQoL can be predicted based on some factors, which are classified into negative and positive factors and have respectively negative and positive effects on QoL (12). **Table.6** provides the factors predicting QoL.

Table-6: Predictors of QoL in Thalassemia.

Predictors of Positive Influence on QOL	References	Predictors of Negative Influence on QOL	References
Evaluate quality of life	[6, 24, 25, 27, 31, 37, 38, 43, 45, 47, 61, 62, 73]	Treatment side effects	[1-3, 27, 28, 30, 35, 37, 38, 42, 43, 47, 49, 50, 53, 54, 57, 58, 62, 65, 67-70]
Oral iron chelator, deferiprone (DFP)	[20, 29, 31, 34, 59, 69, 71]	Subcutaneously administered Deferoxamine (DFO)	[3, 38, 44, 58, 61, 62, 65, 66, 71, 72]
Lower ferritin level	[20, 44, 67]	Iron over load(IOL)	[1, 2, 28, 38, 42, 44, 49, 60, 68]
Provide health education to parents	[27, 45, 46, 51, 57]	Potentially toxic oral agents	[61]
Education about thalassemia	[23, 25, 27, 29, 45, 46, 50, 52, 54, 59]	Daily chelation therapies	[38, 43, 47, 49, 59, 61, 65, 66]
Early diagnosis and start therapy at a younger age	[1, 2, 44, 67]	Delay initiation of transfusion due to delay diagnosis	[2, 44, 67]
Employment	[33, 42]	Unemployment	[33, 42]
Psychosocial support	[5, 20, 23, 24, 27, 30, 33, 38, 42-47, 50-52, 54-56]	Loss of physical function	[1, 33, 42, 47, 49, 65, 67, 69]
Higher level of education	[3, 20, 42, 45, 52, 67, 73]	Low level of education	[5, 42, 45, 67]
Holistic approach and integrated approach	[24, 50]	Family history of thalassemia	[30, 52]

Social function	[5, 25, 58]	Depression and Anxiety	[5, 23, 33, 40, 49, 51, 55, 75]
Religious &spiritual growth	[2, 42, 47, 79]	Fatigue and weakness	[3, 30]
Inter disciplinary health care team	[4, 5, 23, 24, 30, 40, 43, 45, 47, 50, 55, 57, 60, 73, 75]	Chronic pain	[33, 38, 40, 77]
Health promoting behaviours	[27, 30]	Poor self-image and self esteem	[3-5, 42, 62]
Multidisciplinary approach	[33, 40, 42, 45, 46, 57, 60]	Change appearance	[3, 4, 62, 65]
Hematopoietic stem cell transplantation (HSCT)	[26, 74]	Graft versus host disease (GvHD)	[26]
Self –management of thalassemia	[25]	Cardiac disease(heart failure & arrhythmia)	[1, 4, 20, 28, 47, 68]
Management of thalassemia	[25, 42-44, 47, 55, 78]	Delay puberty	[1, 3, 4, 47, 48, 62]
Marriage	[23, 33, 42]	Being single	[23, 33]
Implementing a family center empowerment model	[45]	Marriage and start family	[42]
Alternative complementary medicine	[42]	Endocrine compliance	[1, 48]
Adherence to ICT	[1, 2, 28, 39, 44, 56, 73]	Non adherence to ICT	[1, 3, 23, 39, 44, 48, 72]
Nurse	[5, 23, 50]	Hepatic C	[20]
Gender (females)	[20, 25, 34, 73]		
Support of family	[2, 23, 27, 51, 57, 61]	Poor family income	[20, 34, 35, 52, 56, 65, 67]
Regular follow up	[23, 44, 46, 52, 62, 67]		
Lower age	[20, 23-25, 39, 44, 69]	Higher age and reaching adulthood	[23, 24, 33, 44, 49, 54, 69, 70, 78]
Timely splenectomy , up to 5 years only	[46]	Infertility	[3, 48, 62]
Fewer hospital visit	[3, 62, 65, 67]	Frequent hospital visit	[3, 4, 62, 65, 67]
Cognitive behaviour family therapy(CBFT)	[27]	Glucose metabolism (diabetes)	[4, 68]
DFP/DFX combination	[28]	Depression and anxiety in care givers	[75]
Support of family	[40, 75]	Cost of treatment	[61]
Combine oral chelation	[68]	Hospitalization	[5]
Health care provider	[30, 44, 47-49, 57]	Psychiatric abnormality	[51, 54, 65]
Fewer blood transfusion (<12 per year)	[69]	Multiple organ dysfunction	[38, 51]
Maintaining a pretransfusion hemoglobin level, at least 9-10.5 g/dl or above 7 g/dl	[46, 60]	Lower hemoglobin levels	[30]
Health promoting life style(HPL)	[47]	Uncertainties about future	[4, 65]
Inter personal relations	[47]	infection	[4]
Provision of safe and adequate blood supply	[63]	Blood transfusion	[3, 4, 38, 40, 42, 43, 47, 61-66]
Specialized center	[4, 44]	Increased number of days per week DFO is prescribed	[39]
Early detection complication	[70, 75]	Presence of comorbidities	[2, 23, 49, 54, 67, 72]
Novel therapeutic strategies	[43, 49, 72, 76]	Novel therapeutic strategies	[37, 43, 49, 76]
Nurses enhance their clinical performance and training	[5]		

3-3-6. Being a process or processable

QoL in patients with thalassemia major is a complicated non-linear process. It is integrated, indeterminate, dynamic, interactive, evolutionary, and flexible in nature. It varies from one patient to another patient. The children and adults with thalassemia major experience different symptoms that may affect the quality of their life physiologically and psychologically (6). The process of QoL is designed using four elements though all of them are not necessary. These elements are as follows: dialogue, visions, measurement, and actions. The dialogue refers to making a conversation with a range of people in order to identify patterns in a certain population or group. Visions and conclusions are reached once the dialogue is summarized. Sometimes, instruments or indicators are used instead of visions. If QoL is introduced as a process, it should be measured more than once. Obviously, the time of measurement and variables are determined on the basis of the study perspectives or objectives. Instruments are used in evaluations to reach desirable future. On the contrary, some researchers believe that instruments or indicators are time-consuming, not all people are eligible for answering the instruments or indicators, and they have been developed in proportion to policies and do not show the need for changes in policies. The last element of the process of QoL is an action toward improvement and stability of the individuals' status. All therapeutic and caring actions are developed based on dialogue, visions, and indicators (84). According to the literature, another attribute of QoL in patients with thalassemia major is its processable nature.

4- DISCUSSION

4-1. Consequences

A phenomenon expected to appear following the occurrence of a concept is called a consequence (19). **Table.7** shows the consequences of QoL in patients with thalassemia major.

Table-7: Consequences of QoL in Thalassemia.

Themes	References
Improve physical functioning	[1, 3, 25, 29, 38, 42, 53, 58, 65, 71]
adherence to ICT and optimized treatment	[1, 5, 29, 31, 37, 38, 41-43, 49, 50, 58, 67, 72, 73]
Improve mental conditions	[23, 37, 41, 51, 65, 75, 83]
Self-care & management of disease	[3, 23]
Promotion of education and career	[60, 65]
Promotion of socio-economical situations	[3, 4, 34, 49, 61, 65, 74]
Coping better with this chronic disease state	[3]
Change in their family members' QoL or caregivers	[2, 5, 30, 37, 42, 45, 46, 51, 60, 79]

QoL: Quality of life.

The reduced QoL depicts the pediatric patients' difficulties and sufferings (1). Increased life expectancy, adherence to treatments, receiving regular chelation therapy, reduced iron overload, decreased iron deposition in tissues, especially in the heart and liver, lack of heart failure, and lack of sexual problems directly correlate with HRQoL and are consequences of the increased HRQoL in patients with thalassemia major (1). The enhanced QoL significantly improves the pediatric and adult patients' psychological status (23, 37, 41, 51, 65, 75, 83), and patients make use of more appropriate strategies for coping with stressful situations (3). The patients' improved psychological status leads to the adherence to treatments,

regular use of chelation therapy, a decrease in iron overload, and ultimately, favorable treatment (1, 5, 29, 31, 37, 38, 41, 43, 49, 50, 58, 67, 72, 73). Once the iron overload decreases, the major causes of mortality which are cardiac, liver, and endocrine complications, in these patients, will decrease and the context for doing further activities, educating, having suitable jobs, and marrying will be provided (60, 65). The children and adult patients' economic and social status and eventually motivation and life expectancy improve, as well (3, 4, 34, 49, 61, 65, 74). QoL directly affects the type of treatment and care and screening in children and adult patients with thalassemia major (47, 60).

Regarding the chronic nature of thalassemia, QoL in patients' caregivers is strongly influenced by HRQoL of patients with thalassemia major. The decrease in the patients' HRQoL makes them dependent on their caregivers, and this dependence will reduce the caregivers' QoL. The stress and anxiety caused by treatments, shortage of medications, complications of the disease, and frequent hospitalizations have negative effects on the patients' HRQoL and consequently their caregivers' QoL and cause depression in patients' parents in some cases. Psychological problems in parents and caregivers, stress, anxiety, sadness, apprehension, and feeling of guilt appear more in parents whose child has lower HRQoL (75).

4-1. Study Limitations

Gray studies were excluded from the study due to the global attitude toward thalassemia major. However, the studies were peer-reviewed by a research team, and this raised the validity of this study.

5- CONCLUSION

This concept analysis was performed to recognize the concept of QoL and its dimensions in children with thalassemia major based on Roger's evolutionary method. The concept of QoL in pediatric patients with thalassemia major was evaluated, and the use of this indicator in assessment of the effectiveness of medical therapies and supportive care was discussed in this study. The attention paid to QoL has raised interest in reliable measurement of this indicator. The measurement of QoL and its affectedness has been accepted in the entire course of treatment, since diagnosis and during the long course of treatment and care. The concept of QoL in these pediatric patients is different from that in other people due to the improved treatments and new therapies and the importance of chelators and side effects of blood transfusion. The increased age and life expectancy following new therapies and promotion of care, constant changes in iron overload, supply of new chelators, complications of the disease, family history of thalassemia, economic status, QoL in parents or other caregivers, beliefs and attitudes of parents and caregivers toward the disease were dimensions of the QoL in children with thalassemia major ignored so far.

6- ABBREVIATIONS

QOL	Quality of Life
HRQOL	Health-Related Quality of Life
SF-36	36-Item Short Form Survey
PedsQL	The Pediatric Quality of Life Inventory
B-TM	Beta-thalassemia major
WHO	World Health Organization
PRO's	patient report out come
HPL	Health promoting life style
CBFT	Cognitive behaviour family therapy
DFO	Deferoxamine
DFP	Deferiprone
DFX	Deferasirox
ICT	Iron Chelation Therapy
HSCT	Hematopoietic stem cell transplantation
GvHD	Graft versus host disease
IOL	Iron over load
TranQoL	Transfusion-dependent Quality of Life questionnaire
STQOL	Specific Transfusion Quality of Life

WHOQoL	World Health Organization Quality of Life
CHQ PF-28	Child Health Questionnaire Parent short Form
EQ-5D-3L	Euro Quality of Life five-dimensional 3-level

7- CONFLICT OF INTEREST: None.

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